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ANTI-TUMOR ACTIVITY FROM REPTILE SERUM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of International application PCT/IL02/00590 filed Jul. 18, 2002, the entire content of which is expressly incorporated herein by reference thereto.

FIELD OF THE INVENTION

[0002] The invention relates to anti-cancer agents derived from serum of certain reptiles, to processes for producing same and for the use of these agents in the prevention, treatment, investigation or diagnosis of cancer.

BACKGROUND OF THE INVENTION

[0003] The presence of anti-tumor factors in the serum of mammals has been described in numerous publications in the scientific literature. By way of example, an activity described as tumor necrosis factor, abbreviated as TNF, was detected in the serum of certain mammals including rodents (Cancer Letters 6, 235-240, 1979). This activity was found to be induced by the injection of bacterial endotoxins such as lipopolysaccharide (LPS), or by infection of animals with bacteria that produce such endotoxins. Additional purification and characterization of this activity has disclosed that there are different subtypes of TNF activity, one of the most common forms being referred to as TNF alpha.

[0004] Tumor necrosis factor (TNF α) is a pleiotropic cytokine which has been implicated in immunological and inflammatory responses as well as in pathogenesis of endotoxic and septic shock (Tracey and Lowry, The role of cytokine mediators in septic shock. Adv. Surg. 23, 21-56, 1990). TNF α is one of several cytokines released mainly by mononuclear phagocytic cells in response to various stimuli, including bacterial infection and probably also viral, fungal or parasitic infections.

[0005] Further disclosures involve the isolation and characterization of different polypeptides possessing anti-tumor activity from the sera of mammals including humans, as disclosed for example in U.S. Pat. No. 4,309,418. A human secreted glycoprotein having antitumor activity is disclosed in WO 90/10651.

[0006] Antibodies and their fragments are widely used for therapy and diagnosis of cancers. For example, U.S. Pat. No. 5,169,774 discloses monoclonal anti-human breast cancer antibodies, while U.S. Pat. No. 6,136,311 discloses methods for treatment and diagnosis of cancer using monoclonal antibodies. Methods for imaging and treating bladder cancer using antigen-specific antibody is are disclosed in international application WO 00/12761.

[0007] Several forms of recombinant antibody fragments can be designed to substitute for large intact immunoglobulin molecules. These options include Fab fragments or Fv fragments that are stabilized and/or covalently linked utilizing various strategies (Bird et. al., Science 242, 423-426, 1988).

[0008] Small fragments of antibodies are advantageous for pharmaceutical applications for cancer targeting and imaging for example when small antigen binding molecules are needed to penetrate into large solid tumors.

[0009] International patent application WO 98/17301 discloses peptides derived from shark immunoglobulins for inhibiting retroviruses and for inhibiting growth of tumor cells. The peptide preparations are useful for inhibiting diseases associated with retroviral infection, such as acquired immunodeficiency syndrome. The peptides also inhibit growth of tumor cells, especially sarcomas and leukemias.

[0010] Nowhere is it taught or suggested in the background art that anti-tumor activity may be found in the serum of reptiles, or more specifically in the serum of alligators or crocodiles.

SUMMARY OF THE INVENTION

[0011] The present invention is directed to anti-tumor agents obtained from the serum of certain reptiles. More particularly, the present invention is directed to an anti-tumor agent derived from the serum of alligators or crocodiles.

[0012] The present invention relates to an agent or agents that are polypeptides found in the serum of normal healthy alligators, characterized in that they show specific anti-tumor activity.

[0013] The present invention provides anti-tumor agents derived from the serum of reptiles, comprising at least one serum protein from the serum of normal reptiles.

[0014] According to the present invention, the disclosed agents are able to discriminate between normal proliferating cells and tumor (malignant) cells. This remarkable feature distinguishes the agents of the present invention from common chemotherapeutic agents.

[0015] In one preferred embodiment, the anti-tumor agents of the present invention are immunoglobulin molecules. More preferred molecules according to the present invention are active fragments or domains derived from same immunoglobulin molecules, while additional preferred compounds are peptides derived from the binding sites of such immunoglobulin fragments or domains obtained from reptiles sera.

[0016] The present invention further relates to a process for recovering the activity of the anti-tumor agents in comparatively enriched form by fractionation of alligator serum.

[0017] In one embodiment, the enrichment process comprises the steps of: precipitating proteinaceous material from the serum by partial saturation of the serum with ammonium sulfate; re-dissolving the precipitate and desalting the recovered proteins by dialysis or other suitable means; and fractionating the recovered proteinaceous material by gel filtration, size exclusion chromatography, ion exchange chromatography or the like.

[0018] In yet another embodiment the present invention relates to additional processes enabling purifying the active polypeptides, determining at least part of their amino acid sequence, and characterizing any active domain or domains